Risk Factors Associated with Early vs. Delayed Dementia after Intracerebral Hemorrhage

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Abstract

Importance—Intracerebral hemorrhage (ICH) survivors appear to develop cognitive impairment at high rates, both early after ICH and long-term.

Objective—to identify and compare risk factors for early and delayed dementia after ICH.

Design—longitudinal study enrolling ICH survivors from January 2006 to December 2013.

Setting—tertiary care academic institution.

Participants—1141 individuals with primary ICH, age ≥ 18 years and without pre-ICH dementia were considered for study enrollment. Of these, 24 refused consent and 379 were otherwise ineligible. A total of 738 ICH survivors were therefore included in Early Post-ICH Dementia

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(EPID) analyses. After accounting for incident dementia and mortality at 6 months, 435 participants were included in analyses of Delayed Post-ICH Dementia (DPID).

Exposure(s)—clinical history and demographic information, medications exposure during follow-up. All subjects underwent CT scanning at time of ICH to determine hematoma location and size, as well as severity of CT-defined White Matter Disease (CT-WMD).

Main Outcome and Measure(s)—Cognitive performance was captured using the Modified Telephone Interview for Cognitive Status test. Outcomes included: 1) EPID, diagnosed within 6 months after ICH; 2) DPID, diagnosed beyond 6 months after ICH.

Results—Among 738 ICH survivors, 140 (19%) developed dementia within 6 months. A total of 435 ICH without dementia at 6 months were followed longitudinally (median follow-up 47.4 months, Inter-Quartile Range [IQR] 43.4 - 52.1), with estimated yearly dementia incidence of 5.8% (95%CI 5.1-7.0%). Larger hematoma size (Hazard Ratio [HR] 1.47 per 10cc increase, 95% Confidence Interval [95%CI] 1.09-1.97) and lobar ICH location (HR 2.04, 95% CI 1.06 - 3.91) were specifically associated with EPID, but not with DPID (heterogeneity p<0.05 for both). Educational level (HR 0.60, 95%CI 0.40-0.89), incident mood symptoms (HR 1.29, 95%CI 1.02-1.63), and CT-WMD (HR 1.70, 95%CI 1.07-2.71) were specifically associated with DPID, but not EPID (heterogeneity p<0.05 for all).

Conclusions and Relevance—Early incident dementia after ICH is strongly associated with hematoma size and location. Delayed incident dementia is frequent among ICH survivors, and not prominently associated with acute ICH characteristics. These findings suggest the existence of heterogeneous biological mechanisms accounting for early vs. delayed cognitive decline among ICH survivors.

INTRODUCTION

Intracerebral Hemorrhage (ICH) accounts for 15% of all strokes and ~ 50% of stroke-related associated mortality and disability worldwide.[1,2] ICH survivors are at high risk for several negative outcomes including rebleeding, ischemic stroke, and progressive cognitive impairment. These findings likely reflect the detrimental impact of underlying Cerebral Small Vessel Disease (CSVD), which is presumed to be the etiological factor responsible for both primary ICH and the associated conditions listed above.[3] Indeed, ICH survivors demonstrate higher prevalence of genetic and neuroimaging markers of underlying CSVD than the general elderly population.[4-6]

While progressive cognitive decline (including incident dementia) is frequent after ICH, we possess very limited understanding of its associated risk factors. Prior studies reported very high rates of dementia after ICH, but were unable to fully describe its predictors.[7-10] In particular, they did not investigate whether early and delayed dementias after ICH demonstrate comparable or distinct risk factor profiles.

We hypothesized that the extent of central nervous system injury associated with acute hematoma formation would be strongly associated with Early Post-ICH Dementia (EPID), but confer limited risk for Delayed Post-ICH Dementia (DPID). We sought to test this hypothesis in a ongoing longitudinal study enrolling primary ICH survivors, by means of

two separate analyses focused on: 1) risk of developing dementia within 6 months after acute ICH (EPID); 2) risk of developing dementia 6 months after acute ICH and thereafter (DPID). Risk factors associated with either outcome were tested to clarify whether they conferred risk for cognitive decline only in the early or delayed timeframe.

METHODS

Overall Study Design

In order to investigate whether risk factors for post-ICH dementia differ based on temporal relationship to acute bleeding, we designed a two-stage study format (eFigure 1), including separate analyses for EPID risk (onset within 6 months after ICH), and DPID risk (onset beyond 6 months after ICH). We restricted analyses to individuals surviving beyond 3 months after ICH, in order to limit the impact on cognitive status of unrelated medical and neurological comorbidities leading to early case fatality. We therefore selected the next available follow-up time-point in our study (6 months), to separate EPID from DPID. Participants were first included in the early dementia analyses. Within this group, patients that survived and remained dementia free at 6 months were then included in the delayed dementia risk analyses. Visual inspection of dementia incidence rates supported our study design format by identifying a substantial decrease in incident dementia cases beyond 6 months from index ICH (eFigure 2).

Patient Recruitment and Baseline Data Collection

Participating individuals were enrolled in an ongoing single-center longitudinal cohort study of ICH as previously described.[4,11,12] Particiapnts were selected among consecutive patients age 18 years, admitted to Massachusetts General Hospital (MGH) from January 2006 to December 2013 with primary ICH, i.e. not related to trauma, conversion of an ischemic infarct, rupture of a vascular malformation / aneurysm, or a brain tumor (Figure 1).

All pre-enrollment data were collected via review of existing medical records and billing information, combined with a structured standardized in-person interview. As the primary goal of this study was to investigate incident cognitive decline after ICH, all participants diagnosed with dementia prior to index were excluded. Pre-ICH dementia was identified by administering to reliable informants the 16-item (short) version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). As per reported normative data any subject with an average score of > 3.3 was diagnosed with pre-ICH dementia.[13] In light of known ethnic and racial variations in outcome after ICH,[14] participants were asked at enrollment to self-identify race and ethnicity, choosing from the options recommended for use in research studies by the Office for Management and Budget and the National Institutes of Health. All subjects required and index ICH admission CT scan, obtained within 24 hours of onset of symptoms.

The study protocol was approved by the Massachusetts General Hospital Institutional Review Board. Written informed consent was obtained from all study participants or their surrogates.

Genetic and Neuroimaging Data Acquisition and Interpretation

APOE genotype was determined for subjects consenting to blood draw ccording to previously published methods, to determine number of ε2/ε3/ε4 copies.[4,11] ICH location was assigned based on consensus review of index ICH CT scans by study staff as previously described. [4,11] CT-defined white matter disease (CT-WMD) was quantified using a previously validated 4-point scale, separately grading severity of anterior and posterior WMD as none / mild (grade 0), moderate (grade 1), or severe (grade 2).[4,15,16] MRI with axial gradient-echo images was performed in a subset of patients within 90 days of onset of symptoms, according to previously described methods.[4] On available MRI scans we quantified: 1) MRI-defined White Matter Hyperintensity (MRI-WMH) volume[17]; 2) Cerebral Micro-Bleeds (CMBs) burden and location (lobar vs. non-lobar).[4] All imaging analyses were performed and results recorded by study investigators without knowledge of participating subjects' clinical and/or genetic information.

Longitudinal Follow-up

ICH survivors and/or their caregivers were contacted and interviewed by dedicated study staff at 3 and 6 months after index ICH, and every 6 months thereafter, per established protocols.[4,11,12]. Investigators inquired about and collected medical records pertaining to ICH recurrence, death, functional status, medication regimens according to previously published methods.[12] Cognitive testing was performed at all follow-up times using the Modified Telephone Interview for Cognitive Status (TICS-m) test.[18-22] The TICS-m is validated telephone-based global cognitive assessment tool, that measures overall cognitive performance with scores ranging from 0 (worst performance) to 39 (best performance).[19] We supplemented telephone-based collection of follow-up data with semi-automated review of longitudinal Electronic Medical Records (EMR) as previously described.[4,11,12] Patients who were missing   1 cognitive measurement(s) were excluded based on pre-specified criteria (Figure 1). Subjects' data were censored in case of incident dementia diagnosis, death or loss to follow-up.

Statistical Methods

Variable Definition and Handling—Age at index ICH was analyzed as a continuous variable. Race/ethnicity was analyzed as a categorical variable, with European-American subjects as reference group due to their numerical preponderance. Educational level was dichotomized using a cut-off of   10 years of education.[4] APOE genotype was analyzed using two categorical variables indicating presence of any ε2 or ε4 alleles.[4] CT-defined volumes for index ICH (and intraventricular component, if any) were analyzed as continuous variables. CT-WMD was analyzed as an ordinal variable indicating increasing burden.[4] CMBs counts were analyzed using previously employed cut-off of 0, 1, 2-4, or   5 microbleeds, with separate variables created for lobar and non-lobar CMBs.[4] MRI-WMH volumes were log-transformed and analyzed as a continuous variable. [17]

We defined incident dementia for outcome analyses based on: 1) relevant ICD-9 codes being entered in EMR records and/or 2) subjects assigned TICS-m scores < 20 (based on published normative data).[21,23] We estimated sensitivity and specificity of dementia diagnosis via ICD-9 / TICS-m in comparison to clinical evaluation by the attending

neurologist (when documented in medical records). We performed secondary analyses investigating rate of cognitive decline, which was quantified by calculating individual-specific slopes for TICS-m scores over time and analyzed as a continuous variable.

Statistical Models—We used a time-to-event analysis framework to identify risk factors associated with post-ICH early vs. delayed dementia risk. Separate analyses were conducted risk of EPID and DPID. Risk factors associated with incident dementia (defined as per above), were first assessed in univariable analyses using log-rank tests. Candidate variables for multivariable modeling included all those with $p < 0.20$ for association with incident dementia in univariable analyses. Multivariable analyses employed Cox regression models. Medication exposures were treated as time-varying variables in all Cox regression analyses. After variable selection, a minimal model was generated by backward elimination of non-significant variables ($p > 0.05$). Of note, variables associate with either EPID or DPID risk were included in both multivariable analyses for comparison purposes (even if failing to achieve $p < 0.05$ for association in the parallel analysis). We created multivariable linear regression models to analyze predictors of TICS-m slope as outcome variable. Variable selection procedures for linear regression models were identical to those for Cox regression analyses. Heterogeneity of effects for association of risk factors with early vs. delayed dementia after ICH were evaluated for statically significance using the *metareg* function, part of the *meta* package for the R statistical program.

We addressed multiple testing burden by adopting the False Discovery Rate (FDR) method as developed by Benjamini and Hochberg.[24] All p-values reported are adjusted for multiple testing with the FDR methods. All significance tests were 2-tailed, and significance threshold was set at $p < 0.05$ (after FDR adjustment). All analyses were performed with R software v 3.2.0 (The R Foundation for Statistical Computing).

RESULTS

Study Subjects, Follow-up Information and Dementia Incidence after ICH

A total of 1141 patients age   18 years presented to our center and were diagnosed with primary ICH without pre-existing dementia during the pre-specified enrollment time (Figure 1). Of these, 738 met all eligibility criteria and participated in analyses of early dementia risk after ICH. Of note, 291 of the 379 total excluded patients (77%) were ineligible due to early case fatality (Figure 1). Eligible patients' characteristics are presented in Table 1. Overall, a total of 279/738 (39%) ICH survivors in our study developed dementia. We compared dementia diagnostic accuracy against clinical examination by the attending neurologist in 522/738 (71%) cases with documented cognitive evaluations. Sensitivity and specificity for a TICS-m / ICD-9 based dementia diagnosis were 90% and 94% respectively (compared to in-person evaluation). We observed a total of 55 recurrent ICH events (44 recurrent lobar ICH cases, 11 deep ICH cases), for an overall recurrence rate of 5.2% / year. We repeated all multivariable analyses after removal of recurrent ICH cases with no significant difference in results (eTable 1).

A total of 140 participants (19%) developed incident dementia within 6 months. Among subjects included in these analyses 397 (54%) had available APOE and MRI data for

additional analyses (Table 2). Among the 598 participants who did not develop dementia within 6 months of ICH, 435 were alive at 6 months and therefore eligible delayed dementia incidence analyses. Of these, 257 (59%) had available APOE and MRI data for additional analyses (Table 2). Median longitudinal follow-up duration was 47.4 months (IQR 43.4 - 52.1). Average censoring due to loss to follow-up (other than death or incident dementia) was 1.2% per year. We estimated a yearly dementia incidence rate of 5.8% / year (95%CI 5.1-7.0%), corresponding to 139/435 (32%) diagnoses during follow-up. Cumulative delayed incident dementia rates after ICH are graphically detailed in Figure 2. Based on findings reported above, EPID (140 of 279 dementia cases) and DPID (139 of 279 dementia cases) accounted for approximately 50% of diagnoses each.

Risk Factors for Early Incident Dementia after ICH

We initially performed univariable analyses to identify associations between characteristics listed in Table 1 and EPID risk, and selected for further multivariable modeling (univariable $p < 0.20$) age at index ICH, African-American ethnicity, ICH location, and ICH volume. Multivariable analyses results are presented in Table 3 (Model 1), with additional risk factors associated with DPID risk included for comparison purposes. Significant associations with EPID risk included age at index ICH, ICH location, and ICH volume. We repeated univariable and multivariable analyses including APOE and MRI data listed in Table 2 in the smaller groups of ICH survivors with these data points available (n = 397). In multivariable analyses (Table 3, Model 2) an additional significant association with EPID risk was uncovered for the APOE ε2 variant.

Risk Factors for Delayed Incident Dementia after ICH

Univariable analyses of DPID risk identified significant associations with age at index ICH, educational level, African-American ethnicity, diagnosis of mood disorder, and increasing CT-WMD severity (all $p < 0.05$). All these associations were confirmed in multivariable analysis, as detailed in Table 3, Model 1 (as above, additional risk factors associated with EPID risk are included for comparison purposes only). We separately included APOE and MRI data in univariable and multivariable analyses (n = 257), as presented in Table 3 (Model 2); in these analyses we uncovered additional significant associations with DPID risk for: 1) increasing burden of lobar CMBs; 2) the APOE ε4 variant.

Comparison of Risk Factors for Early and Delayed Dementia after ICH

We formally compared risk factors profiles for EPID vs. DPID, as presented in detailed in Table 3 (Heterogeneity; right-most column). Among all identified risk factors, the following showed statistically significant ($p < 0.05$) preferential association with early incident dementia: ICH volume, lobar ICH location, and the APOE ε2 variant. Conversely, educational level, diagnosis of mood disorder, increasing CT-WMD severity, increasing lobar CMBs burden and the APOE ε4 variant were specifically associated with delayed dementia risk, but not with EPID diagnosis. Of all identified risk factors, only advancing age at index ICH represented a shared risk factor for both early and delayed incident dementia after ICH. We performed secondary comparative analyses of cognitive decline rates before vs. after 6 months post-ICH (eTable2). ICH volume and lobar ICH location were confirmed as spefically associated with cognitive decline rate before 6 months post-ICH, while

educational level, diagnosis of mood disorder, and increasing CT-WMD severity were specifically associated with cognitive decline rate after 6 months post-ICH (all heterogeneity $p < 0.05$).

DISCUSSION

We conducted the first comprehensive longitudinal study of cognitive impairment after primary ICH, leveraging a large cohort of consecutive cases with in-depth characterization and extended follow-up to demonstrate a high incidence of dementia after primary intraparenchymal hemorrhage. Of great interest, we showed those early and delayed dementias were closely matched in incidence. We also demonstrated a significant discrepancy in risk factor profile between EPID and DPID risks; the former was primarily associated with acute hematoma parameters (location and size), whereas the latter was not. These findings support the hypothesis that different mechanisms underlie cognitive impairment after ICH, depending on temporal dynamics.

Post-ICH dementia rate derived from our analyses are substantial, particularly as all dementia diagnoses were incident during follow-up. Removal of the small number of subjects experiencing recurrent ICH did not lower cognitive decline rates substantially. As mentioned above, far from being a limited occurrence, incident dementia among ICH survivors free of dementia at 6 months accounts for half of all cases. These findings are of immediate clinical relevance to healthcare providers and ICH survivors. Assuming replication of our findings in future studies, adequate communication of cognitive decline risk (especially beyond the immediate post-ICH period) will represent a critical issue for clinicians, their ICH patients and family / caregivers.

Previous studies of cognitive impairment after ICH or hemorrhagic stroke have been limited in their ability to disentangle the impact on cognitive outcomes of the acute bleeding event vs. potential underlying disease processes.[7-10] As a result, identified predictors of cognitive performance (other than age), were primarily hematoma size and location. We have indeed confirmed that these variables are strongly associated with EPID risk, likely reflecting cortical areas or networks directly damaged by acute bleeding. By virtue of our study design (and due to the study's large sample size and long follow-up) we were able to demonstrate that DPID risk has little to no association with the acute bleeding event.

Indeed, we identified several CSVD-related markers and risk factors (APOE ε4, WMD and CMBs) as associated with DPID risk. The known association between CSVD and ICH may represent the underlying unifying etiological factor explaining the aforementioned results, but we are unable to further address this question in our analyses. Of note, we identified opposite associations patterns for the ε2 and ε4 variants of the APOE gene. We previously showed that the APOE ε2 variant is associated with larger hematoma volume and/or hematoma expansion, and thus with worse functional outcome at 3 months.[25,26] It seems likely that, having adjusted only for initial hematoma volume in our analyses, the known association with hematoma expansion risk accounts for its relationship with EPID incidence. In contrast, the APOE ε4 variant is known to increase amyloid burden in both the brain

parenchyma and vasculature, and is more likely to exert a long-term effect on cognitive outcome after ICH.[27,28]

Our study has limitations. Firstly, the vast majority of our cognitive outcome information was obtained using the TICS-m tool for phone-based cognitive evaluations, rather than in-person interviews. The TICS-m, however, has been validated multiple times as reliable, efficient tool for global cognitive assessment.[18-22] TICS-m scores have been shown in multiple prior studies to correlate closely with in-person testing scores (e.g. Mini-Mental State Examination [MMSE] or Montreal Cognitive Assessment [MoCA]), and to diagnose dementia with high sensitivity and specificity.[19-22] Only a small percentage of ICH survivors were unable to complete one or more TICS-m questionnaires, and were therefore excluded or censored. We also observed excellent concordance between TICS-m dementia diagnoses and in-person clinical evaluations. Secondly, although we detected an association between self-reported African-American racial background and cognitive decline after ICH, it is possible that other minority groups may be also at higher risk of post-ICH cognitive impairment. However, their inadequate representation in this cohort likely limited power to uncover such associations. Third, because of our follow-up frequency we had limited ability to capture precise timing of dementia onset, particularly for EPID. Finally, we cannot exclude the possibility that Alzheimer's disease pathology plays a role in the observed findings. Indeed, all CSVD-related markers associated with DPID risk in our analyses have previously been observed in Late-Onset Alzheimer's Disease (LOAD) patients.[29-31] Additional studies will be required to better clarify the contribution of LOAD to cognitive decline after ICH.

In summary, we identified a substantial risk of incident cognitive decline among ICH survivors in the first large, comprehensive longitudinal study on the topic. In the short-term, within 6 months of ICH, we confirmed that hematoma location and volume are strongly associated with incident dementia risk. However, we diagnosed at least half of dementia cases beyond the 6 months mark, and demonstrated the existence of a significantly different risk factor profile. This latter group of patients will benefit from additional studies investigating the pathophysiology of long-term cognitive decline after ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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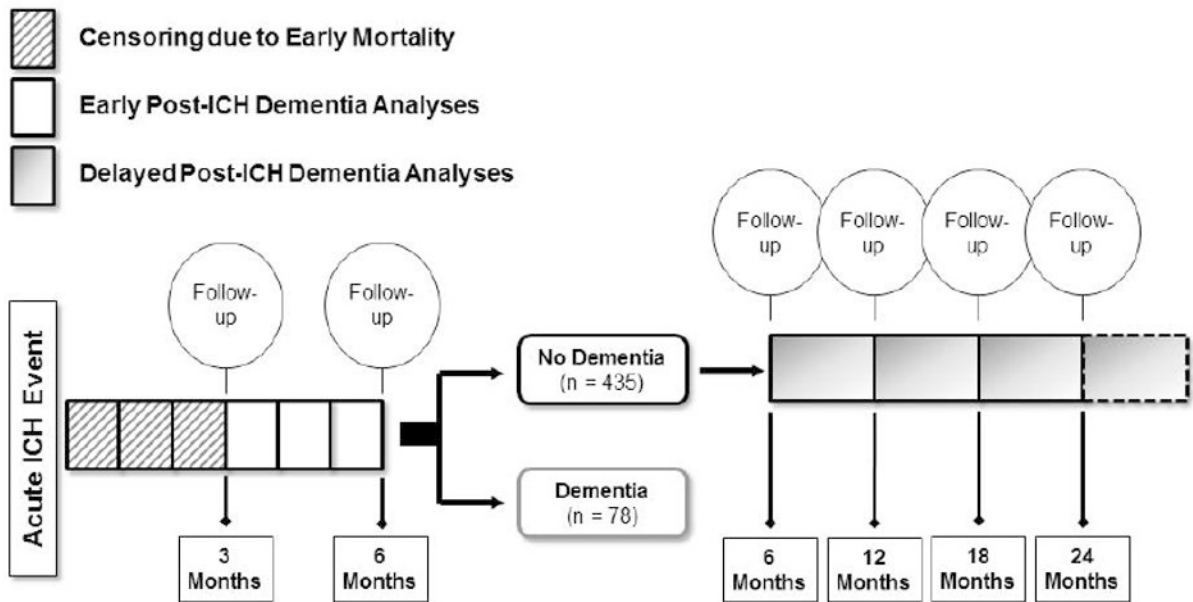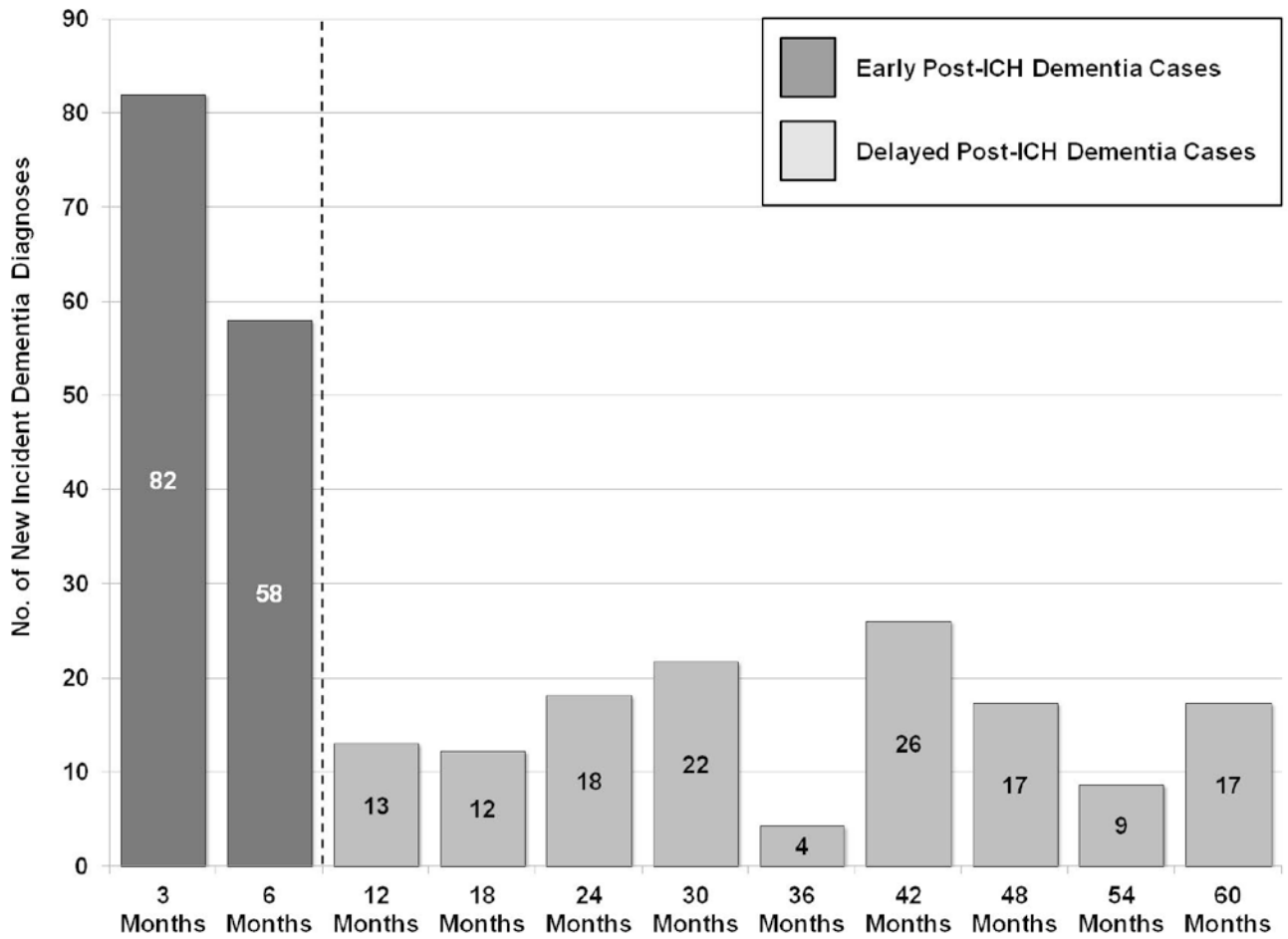
Figure 1. Study Design and Inclusion / Exclusion Criteria

Figure presents study design, inclusion / exclusion criteria and patient groups retained for analysis. Solid single-line boxes represent subjects meeting criteria for inclusion in the present study at each step. Eligibility criteria for inclusion in the study are listed in grey-background boxes. Dashed lines connect to dashed-bordered boxes listing criteria for exclusion and number of subjects excluded. Double-line bordered boxes indicate study group subsets selected for analyses mentioned in the Results section. Oval shapes with bolded margins identify planned analyses.

Abbreviations: ICH = Intracerebral Hemorrhage

Figure 2. Incident Delayed Cognitive Decline among ICH Survivors
Cumulative incidence of Delayed Post-ICH Dementia (DPID), expressed as percentages of total study population. Rates comp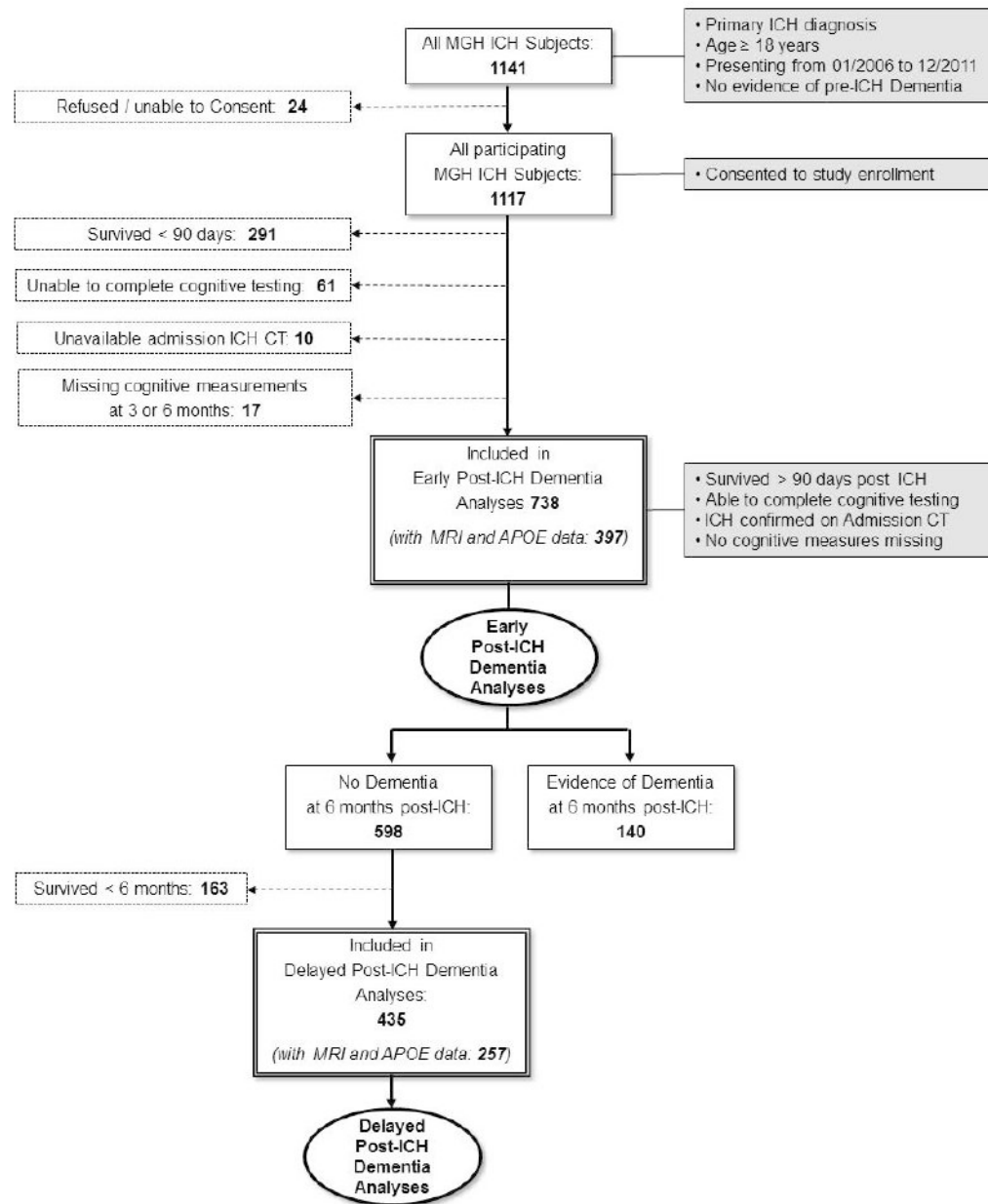uted among all study participants that were free of dementia at 6 months. Number of patients alive and being followed at each time point is listed at the bottom. Legend located in left lower corner.
Abbreviations: ICH = Intracerebral Hemorrhage

Table 1

Cohort Characteristics

Variables	All ICH Survivors		ICH Survivors with no Dementia at 6 months	
	No. 738	% 100	No. 435	% 100
Demographics				
Age at Enrollment (Mean, SD)	74.3 (12.1)	-	71.2 (11.3)	-
Sex (Male)	384	52	226	52
Race / Ethnicity				
- European American	605	82	331	76
- African American	74	10	65	15
- Asian American	21	3	15	3
- Hispanic	23	3	13	3
- Other	15	2	11	3
Education (10 years)	465	63	222	51
Past Medical History (at Time of Enrollment)				
Hypertension	546	74	305	70
Ischemic Heart Disease	133	18	65	15
Atrial Fibrillation	118	16	39	9
Diabetes	125	17	65	15
Mood Disorder	111	15	78	18
Anxiety Disorder	52	7	52	12
Prior lobar ICH	15	2	13	3
Prior non-lobar ICH	7	1	1	0.2
Prior Ischemic Stroke / TIA	31	4	20	5
CT Imaging Data				
ICH Location				
- Lobar	289	39	187	43
- Deep	359	49	204	47
- Cerebellar	69	9	26	6
- Multiple Locations	21	3	18	4
ICH Volume (Median, IQR)	19.4 (4.5 - 24.1)	-	17.8 (3.9 - 25.0)	-
Intraventricular Extension	214	29	117	27
CT-WMD Presence	494	67	318	73
Post-ICH Medication Use				
Antiplatelet agents	103	14	65	15
Warfarin	74	10	39	9
Statins	258	35	157	36
Antihypertensive Agents	435	59	291	67
SSRI	207	28	117	27

Abbreviations: ICH = Intra-Cerebral Hemorrhage, IQR = Inter-Quartile Range, SD = Standard Deviation, SSRI = Selective Serotonin Reuptake Inhibitor Antidepressants, CT-WMD = CT-defined White Matter Disease, TIA = Transient Ischemic Attack.

Table 2

Genetic and MRI data for participating individuals

Variables	All ICH Survivors		ICH Survivors with no Dementia at 6 months	
	No. 397	% 100	No. 257	% 100
MRI Imaging Data				
Cerebral MBs (Presence)				
- Any location	270	68	180	70
- Strictly Lobar	123	31	86	33
- Strictly Deep	111	28	70	27
- Mixed	36	9	24	9
CMBs Count (Any Location)				
- 0	127	32	77	30
- 1 or 2	92	23	62	24
- 2 to 4	79	20	51	20
- 5	99	25	67	26
MRI-WMH Volume	17.4		15.8	
(Median, IQR in cc)	(7.2 - 35.1)	-	(7.3 - 28.9)	-
APOE Genotype				
APOE ε2 (Minor Allele Frequency)	0.11	-	0.08	-
APOE ε4 (Minor Allele Frequency)	0.17	-	0.20	-

Abbreviations: APOE = Apolipoprotein E Gene, CMBs = Cerebral Microbleeds, ICH = Intra-Cerebral Hemorrhage, IQR = Inter-Quartile Range, MRI-WMH = MRI-defined White Matter Hyperintensity.

Table 3

Multivariable Analyses of Risk Factors for Early vs. Delayed Dementia Incidence after ICH

Model 1 (Includes: Demographics, Medical History and CT Imaging Data)*	Early Post-ICH Dementia Risk (n = 619)			Delayed Post-ICH Dementia Risk (n = 435)			Heterogeneity p-value
	HR	95% CI	p	HR	95% CI	p	
Age	1.02	1.00 – 1.04	0.034	1.01	1.00 - 1.01	0.049	0.78
Education (≥ 10 years)	0.89	0.61 – 1.30	0.55	0.60	0.40 – 0.89	0.012	<0.001
Race: African American	1.22	0.96 – 1.55	0.11	1.48	1.09 – 2.02	0.014	0.55
Mood Disorder	0.66	0.04 – 11.11	0.77	1.29	1.02 - 1.63	0.036	0.012
ICH Volume (per 10 cc increase)	1.47	1.09 – 1.97	0.011	1.10	0.70 – 1.73	0.68	< 0.001
ICH Location: Lobar	2.04	1.06 – 3.91	0.033	1.33	0.25 – 7.03	0.74	0.024
CT-WMD Severity	1.34	0.23 – 7.76	0.74	1.70	1.07 - 2.71	0.027	0.044

Model 2 (Includes: Model 1 data, APOE Genotype and MRI Imaging Data)†	Early Post-ICH Dementia Risk (n = 397)			Delayed Post-ICH Dementia Risk (n = 257)			Heterogeneity p-value
	HR	95% CI	p	HR	95% CI	p	
Age	1.02	1.00 – 1.04	0.011	1.01	1.00 - 1.01	0.032	0.94
Education (≥ 10 years)	1.12	0.82 – 1.54	0.48	0.57	0.36 – 0.90	0.016	<0.001
Race: African American	1.42	0.64 – 3.17	0.39	1.39	1.07 – 1.81	0.015	0.42
Mood Disorder	0.59	0.13 – 2.77	0.51	1.56	1.11 – 2.19	0.011	0.006
ICH Volume (per 10 cc increase)	1.52	1.12 – 2.07	0.008	0.89	0.58 – 1.37	0.60	<0.001
ICH Location: Lobar	1.66	1.01 – 2.73	0.047	1.19	0.46 – 3.09	0.72	0.19
CT-WMD Severity	0.89	0.54 – 1.36	0.52	1.70	1.07 - 2.71	0.027	0.011
APOE ε2 (1+ copies)	1.69	1.14 – 2.50	0.009	1.29	0.79 – 2.10	0.31	0.031
APOE ε4 (1+ copies)	1.06	0.68 – 1.64	0.80	2.12	1.45 - 3.09	<0.001	0.002
CMBs (Lobar)	0.82	0.26 – 2.62	0.74	1.78	1.07 - 2.98	0.029	0.042

Table presents detailed results of multivariable analyses only, please refer to Methods section for information on univariable testing for association. Results shown only for variables significantly associated with early and/or delayed dementia risk, and thus selected for heterogeneity of effects testing. Heterogeneity p-values < 0.05 indicate statistically significant differences in effects sizes for a certain variable when comparing its association with early vs. delayed post-ICH dementia risk.

*
Patients' characteristics screened via univariable comparisons for inclusion in multivariable analysis are listed in Table 1.

†
Patients' characteristics screened via univariable comparisons for inclusion in multivariable analysis were those entered in Model 1 (see above), and genetic and MRI data listed in Table 2. These analyses were restricted to participants with available genotype and MRI data (Table 2).

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Abbreviations: 95% CI = 95% Confidence Interval, APOE = Apolipoprotein E Gene, CMBs = Cerebral Microbleeds, CT-WMD = CT-defined White Matter disease, HR = Hazard Ratio, ICH = Intracerebral Hemorrhage, IVH = Intraventricular Hemorrhage.